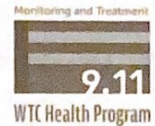


## Petition for the Addition of a New WTC-Related Health Condition for Coverage under the World Trade Center (WTC) Health Program



U.S. Department of Health and Human Services  
Centers for Disease Control and Prevention  
National Institute for Occupational Safety and Health

### General Instructions

Any interested party may petition the WTC Program Administrator to add a condition to the List of WTC-Related Health Conditions (List) in 42 C.F.R. Part 88 (see <http://www.cdc.gov/wtc/faq.html#hlthcond> for the complete list).

Please use this form to petition the Administrator to add a health condition (any recognized medical condition requiring treatment or medication) to the List. Please use a separate form for each health condition.

Use of this petition *form* is voluntary, but any petition must include all of the information identified below, as required by 42 C.F.R. Part 88. Petitions that do not provide the required information will not be considered by the WTC Program Administrator. Additional supporting materials may be submitted and are encouraged.

Please note, however, the petition and all supporting materials submitted to the WTC Health Program are part of the public record and may be subject to public disclosure. Personal information will be redacted prior to public disclosure.

Please TYPE or PRINT all information clearly on the form.

If you need more space to provide the required information, please attach additional pages to this form.

Mail or email this form to: World Trade Center Health Program  
395 E. Street, S.W., Suite 9200  
Washington, D.C. 20201  
[WTC@cdc.gov](mailto:WTC@cdc.gov)

Public reporting burden of this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to CDC/ATSDR Information Collection Review Office, 1600 Clifton Road NE, MS D-74, Atlanta, Georgia 30333; ATTN: PRA (0920-0929).

**A. Interested Party Information**

**A1. Do you represent an organization (are you submitting this petition on behalf of an organization)?**

Yes (Go to A2)  No (Go to A3)

**A2. Organization Information:**

Name of organization

**A3. Name of Individual Petitioner or Organization Representative:**

First name

Last name

(on behalf of husband who is a WTC first responder)

Position, if representative of organization

**A4. Mailing Address:**

Street

City

State

Zip code

**A5. Telephone Number:**

**A6. Email Address:**

**B. Proposed WTC-Related Health Condition Information**

**B1. Health Condition Information:**

Cardiovascular Disease

Name of health condition you wish to petition to add to the List of covered conditions

If the name of the condition is not known, please provide a description of the condition or the name of the diagnosis provided by a physician or other healthcare provider.

**C. Basis for Proposing that the Condition Be Added to the List of WTC-Related Health Conditions**

**C1. Describe the reasons the WTC Program Administrator should consider the addition of this health condition. Explain how the health condition you are proposing relates to the exposures that may have occurred from the September 11, 2001, terrorist attacks. Your explanation must include a medical basis for the relationship/association between the 9/11 exposure and the proposed health condition. The medical basis may be demonstrated by reference to a peer-reviewed, published, epidemiologic study about the health condition among 9/11 exposed populations or to clinical case reports of health conditions in WTC responders or survivors. First-hand accounts or anecdotal evidence may not be sufficient to establish medical basis. If you need more space, please attach additional pages to this form.**

See Attached

#### D. Signature of Petitioner

Sign your name below to indicate that you are petitioning the WTC Program Administrator to consider adding a health condition to the list of WTC-related health conditions identified in 42 C.F.R. Part 88.

Signature

Date

#### Privacy Act Statement

In accordance with the Privacy Act of 1974, as amended (5 U.S.C. § 552a), you are hereby notified of the following:

Title I of the James Zadroga 9/11 Health and Compensation Act of 2010 amended the Public Health Service Act (PHS Act) to establish the World Trade Center (WTC) Health Program. Sections 3311, 3312, and 3321 of Title XXXIII of the PHS Act require that the WTC Program Administrator develop regulations to implement portions of the WTC Health Program established within the Department of Health and Human Services (HHS). The WTC Health Program is administered by the Director of the National Institute for Occupational Safety and Health (NIOSH), within the Centers for Disease Control and Prevention (CDC). The information provided with this form and supporting documentation will be used by the WTC Program Administrator to consider the disposition of a petitioned-for health condition. Disclosure of this information is voluntary.

Records containing information in identifiable form become part of an existing NIOSH system of records under the Privacy Act, 09-20-0147, "Occupational Health Epidemiological Studies and EEOICPA Program Records and WTC Health Program Records, HHS/CDC/NIOSH." These records are treated in a confidential manner, unless otherwise compelled by law.

Information submitted to WTC Health Program which may be considered "protected health information" pursuant to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (Pub. L. 104-191; 42 U.S.C. § 1320d) and the HIPAA Privacy, Security, Breach Notification, and Enforcement Rules (45 C.F.R. pts. 160, 162, and 164) will be maintained in accordance with all applicable laws.

NIOSH may disclose information in identifiable form only insofar as such disclosure is permitted pursuant to the HIPAA Privacy Rule; this may include disclosure to the WTC Health Program Scientific/Technical Advisory Committee (STAC), which may be asked to consider the petition and issue a recommendation to the WTC Program Administrator. Information in identifiable form will be redacted from submitted petition forms and supporting documentation that become a part of the public record (e.g. in conjunction with STAC consideration or a rulemaking).

**Petition for the Addition of a New WTC-Related Health Condition for Coverage under the  
World Trade Center (WTC) Health Program**

**C. Basis for Proposing that the Condition Be Added to the List of WTC-Related Health Conditions**

The WTC first responder petitioning for inclusion of cardiovascular disease as a WTC-certified health condition spent over 600 combined hours working at the WTC site, Fresh Kills Landfill, and the barges. He has been diagnosed with multiple WTC-certified physical and mental health conditions. In December 2022, he was diagnosed with a myocardial infarction while hospitalized for the treatment of a current WTC-certified illness. Medical records are available to facilitate the addition of cardiovascular disease as a WTC-certified condition, but even with the omission of sensitive information, he prefers to maintain his health privacy and not publicize any health information.

There is a growing body of research from both human and in vivo studies that there is a causal relationship between exposure to toxic substances at the WTC and associated sites and the development of cardiovascular disease. Another first responder previously submitted a petition for the addition of cardiovascular disease as a WTC-certified health condition on March 7, 2014, (Petition 004) but it was denied based on insufficient evidence (Federal Register, Vol. 79, No. 87, pg. 25766-25767, May 6, 2014). Per the determination of the WTC Program Administrator from this prior petition, cardiovascular disease includes a heart attack, acute or chronic coronary artery disease, cardiac arrhythmia, angina, and any other heart condition. A literature search was performed for this new petition for research on the association of exposure to WTC toxins to cardiovascular disease on or after the submission of the prior petition. This literature search yielded a total of nine human research, peer-reviewed studies and three in-vivo, peer-reviewed studies.

Studies from the literature search provide relevant, high-quality evidence of the causal relationship between exposure to WTC toxins and cardiovascular disease. Cohen et. al (2019) performed one of the most robust studies demonstrating this relationship. Researchers utilized a large study population of almost 10,000 WTC first responders. Researchers obtained outcome measures from physician-documented diagnoses, rather than relying solely on self-reported diagnoses, which was one limitation determined from the petition denial in 2014. Results of this large-scale study were that the WTC first responder study population was at increased risk for developing cardiovascular disease long-term. Another study by Sloan et al. (2021) examined a general WTC responder population of approximately 90, 000 individuals and determined that those who responded on 9/11/2001 had a higher risk for developing cardiovascular disease compared to those who responded afterwards, indicating an association between intensity of exposure to WTC toxins and the development of cardiovascular disease.

Two of the studies address the causal relationship between other current WTC-certified medical and mental health conditions with cardiovascular disease. One study by Iyengar-Kapuganti et al. (2022) concluded that there was a strong positive association between obstructive sleep apnea (OSA) and cardiac dysfunction, specifically left ventricular diastolic dysfunction (LVDD). Another study by Remch et al. (2018) found that post-traumatic stress disorder (PTSD) increases the risk for myocardial infarction (MI). Rather than being confounding factors, these studies display the interconnectedness of cardiovascular disease to other WTC-certified health conditions. OSA is the fifth top WTC-certified health condition, while PTSD is the sixth (CDC, 2022). The reference by Mears et al. (2022) is a

## Cardiovascular Disease Petition 1-2023

systematic review of WTC-exposed populations and adverse health effects, including cardiovascular disease. Studies by Koshy et al. (2017) and Moline et al. (2016) revealed increased cardiometabolic effects in two WTC-exposed populations, adolescents and law enforcement officers. A 2017 study conducted by Alper et al. determined a dose-response association between WTC dust exposure and heart disease. Finally, three in-vivo studies determined a positive correlation between WTC-toxin exposure and cardiac dysfunction (Park et al., 2022; Tanwar et al., 2019; Veerappan et al., 2020).

The body of evidence linking cardiovascular disease to WTC toxins as well as to current WTC-certified health conditions has increased since the original petition to add cardiovascular disease for coverage under the WTC Health Program was presented in 2014. Those exposed to WTC toxins cannot afford to wait another 10 years for additional research to emerge to obtain health coverage for cardiovascular disease through the WTC Health Program. It is imperative that the WTC Health Program add cardiovascular disease now as a certified medical condition so that program participants may receive the appropriate medical services to decrease long-term morbidity and mortality.

Centers for Disease Control. (June 2022). *World Trade Center Health Program: Top 10 certified conditions*. [https://www.cdc.gov/wtc/ataglance\\_2022\\_0630.html](https://www.cdc.gov/wtc/ataglance_2022_0630.html)

## Reference List with Study Summaries

### Peer-Reviewed Human Research: Cardiovascular Disease in WTC-Exposed Populations

#### 1. Injury, Intense Dust Exposure, and Chronic Disease Among Survivors of the World Trade Center Terrorist Attacks of September 11, 2001

Alper, H. E., Yu, S., Stellman, S. D. et al. Injury, intense dust exposure, and chronic disease among survivors of the World Trade Center terrorist attacks of September 11, 2001. (2017). *Inj. Epidemiol*, 4, 17. <https://doi.org/10.1186/s40621-017-0115-x>

#### Abstract

**Background:** The World Trade Center attack of September 11, 2001, in New York City (9/11) exposed thousands of people to intense concentrations of hazardous materials that have resulted in reports of increased levels of asthma, heart disease, diabetes, and other chronic diseases along with psychological illnesses such as post-traumatic stress disorder (PTSD). Few studies have discriminated between health consequences of immediate (short-term or acute) intense exposures versus chronic residential or workplace exposures.

**Methods:** We used proportional hazards methods to determine adjusted hazard ratios (AHRs) for associations between several components of acute exposures (e.g., injury, immersion in the dust cloud) and four chronic disease outcomes: asthma, other non-neoplastic lung diseases, cardiovascular disease, and diabetes, in 8701 persons free of those conditions prior to exposure and who were physically present during or immediately after the World Trade Center attacks. Participants were followed prospectively up to 11 years post-9/11.

**Results:** Heart disease exhibited a dose-response association with sustaining injury (1 injury type: AHR = 2.0, 95% CI (Confidence Interval) 1.1–3.6; 2 injury types: AHR = 3.1, 95% CI 1.2–7.9; 3 or more injury types: AHR = 6.8, 95% CI 2.0–22.6), while asthma and other lung diseases were both significantly associated with dust cloud exposure (AHR = 1.3, 95% CI 1.0–1.6). Diabetes was not associated with any of the predictors assessed in this study.

**Conclusion:** In this study we demonstrated that the acute exposures of injury and dust cloud that were sustained on 9/11/2001 had significant associations with later heart and respiratory diseases. Continued monitoring of 9/11 exposed persons' health by medical providers is warranted for the foreseeable future.

#### 2. Long-term Cardiovascular Disease Risk Among Firefighters After the World Trade Center Disaster

Cohen H. W., Zeig-Owens R., Joe, C., et al. (2019). Long-term cardiovascular disease risk among firefighters after the World Trade Center disaster. *JAMA Netw Open*, 2(9). doi:10.1001/jamanetworkopen.2019.9775

#### Key Points

**Question:** Is World Trade Center exposure on and after September 11, 2001, associated with long-term cardiovascular disease risk in Fire Department of the City of New York firefighters?

**Findings:** In this cohort study of 9796 firefighters, age-adjusted incident rates of cardiovascular disease were higher for firefighters with greater World Trade Center exposure. Both acute World Trade Center as well as repeated exposure during 6 or more months at the World Trade Center site appeared to be associated with long-term elevated cardiovascular disease risk.

**Meaning:** These findings suggest the continued need for long-term monitoring of the health of survivors of disasters.

### **Abstract**

**Importance:** Published studies examining the association between World Trade Center (WTC) exposure on and after September 11, 2001, and longer-term cardiovascular disease (CVD) outcomes have reported mixed findings.

**Objective:** To assess whether WTC exposure was associated with elevated CVD risk in Fire Department of the City of New York (FDNY) firefighters.

**Design, Settings, and Participants:** In this cohort study, the association between WTC exposure and the risk of CVD was assessed between September 11, 2001, and December 31, 2017, in FDNY male firefighters. Multivariable Cox regression analyses were used to estimate CVD risk in association with 2 measures of WTC exposure: arrival time to the WTC site and duration of work at the WTC site. Data analyses were conducted from May 1, 2018, to March 8, 2019.

**Main Outcomes and Measures:** The primary CVD outcome included myocardial infarction, stroke, unstable angina, coronary artery surgery or angioplasty, or CVD death. The secondary outcome (all CVD) included all primary outcome events or any of the following: transient ischemic attack; stable angina, defined as either use of angina medication or cardiac catheterization without intervention; cardiomyopathy; and other CVD (aortic aneurysm, peripheral arterial vascular intervention, and carotid artery surgery).

**Results:** There were 489 primary outcome events among 9796 male firefighters (mean [SD] age on September 11, 2001, was 40.3 [7.4] years and 7210 individuals [73.6%] were never smokers). Age-adjusted incident rates of CVD were higher for firefighters with greater WTC exposure. The multivariable adjusted hazard ratio (HR) for the primary CVD outcome was 1.44 (95% CI, 1.09-1.90) for the earliest arrival group compared with those who arrived later. Similarly, those who worked at the WTC site for 6 or more months vs those who worked less time at the site were more likely to have a CVD event (HR, 1.30; 95% CI, 1.05-1.60). Well-established CVD risk factors, including hypertension (HR, 1.41; 95% CI, 1.10-1.80), hypercholesterolemia (HR, 1.56; 95% CI, 1.28-1.91), diabetes (HR, 1.99; 95% CI, 1.33-2.98), and smoking (current: HR, 2.13; 95% CI, 1.68-2.70; former: HR, 1.55; 95% CI, 1.23-1.95), were significantly associated with CVD in the multivariable models. Analyses with the all-CVD outcome were similar.

**Conclusions and Relevance:** The findings of the study suggest a significant association between greater WTC exposure and long-term CVD risk. The findings appear to reinforce the importance of long-term monitoring of the health of survivors of disasters.

### 3. Obstructive Sleep Apnoea and Left Ventricular Diastolic Dysfunction Among First Responders to the 9/11 World Trade Center Terrorist Attack: A Cross-Sectional Study

Iyengar-Kapuganti R. L., Maceda, C. S., Croft, L. B., et al. (2022). Obstructive sleep apnoea and left ventricular diastolic dysfunction among first responders to the 9/11 World Trade Center terrorist attack: A cross-sectional study. *BMJ Open*, 2022, 12: e058366. doi: 10.1136/bmjopen-2021-058366

#### Abstract

**Objectives** Obstructive sleep apnoea (OSA) is often linked to cardiovascular disease. A limited number of studies have reported an association between OSA and left ventricular diastolic dysfunction (LVDD). However, prior studies were performed on small patient populations. Studies have shown a high prevalence of OSA among first responders to the 9/11 World Trade Center (WTC) terrorist attack. We investigated the relationship between OSA and LVDD in a large population of WTC responders.

#### Design: Cross-sectional study.

**Setting** One-time screening program as part of the WTC-CHEST Study (NCT10466218), performed at a quaternary medical center in New York City, from November 2011 to June 2014.

**Participants:** A total of 1007 participants with mean age of 51 years of mostly non-Hispanic white men were evaluated. Patients from the WTC Health Program-Clinical Center of Excellence, who were over the age of 39 years, were eligible to participate.

**Results:** Evaluation of those without OSA diagnosis showed no significant association with LVDD when comparing those screened (Berlin Questionnaire) as OSA high risk versus OSA low risk ( $p=0.101$ ). Among those diagnosed with LVDD, there was a significant association when comparing those with and without patient reported OSA (OR 1.50, 95% CI 1.13 to 2.00,  $p=0.005$ ), but the significance was not maintained after adjusting for pertinent variables (OR 1.3, 0.94 to 1.75,  $p=0.119$ ). Notably, comparing those with OSA diagnosis and those low risk of OSA, the OR for LVDD was significant (1.69, 1.24 to 2.31,  $p=0.001$ ), and after adjusting for waist-hip ratio, diabetes and coronary artery calcium score percentile, the relationship remained significant (OR 1.45, 1.03 to 2.04,  $p=0.032$ ).

**Conclusion:** The strong association of OSA with LVDD in this population may inform future guidelines to recommend screening for LVDD in high-risk asymptomatic patients with OSA.

### 4. Exposure to Particulate Matter in World Trade Center Law Enforcement and Its Relationship to Cardiovascular Risk

Iyengar R, Maceda C, McLaughlin M, et al. (2017). Exposure to particulate matter in World Trade Center law enforcement and its relationship to cardiovascular risk. *J Am Coll Cardiol*, Mar, 69 (11\_Supplement). [https://doi.org/10.1016/S0735-1097\(17\)35170-7](https://doi.org/10.1016/S0735-1097(17)35170-7)

#### Introduction

**Background:** Exposure to particulate matter (PM) is a risk factor for cardiovascular disease (CVD). Different mechanisms, including inflammatory processes, are responsible for acute and chronic toxic effects. First responders during the World Trade Center (WTC) tragedy were exposed to PM leading to potential increased CVD risk. We aim to see if there is an interaction over time related to increased CVD risk from exposure to PM.

**Methods:** We evaluated 356 participants three discrete WTC screening events. All participants were law enforcement officers who participated in rescue and recovery at Ground Zero. CVD 10-year risk was calculated using Framingham Risk Score. WTC exposure scores were defined as three exposure groups (XP3) and four exposure groups (XP4). ANOVA and generalized linear model in repeated measures analysis were performed in SAS 9.4.

**Results:** Analysis between CVD risk and exposure in XP3 (Table 1A) and XP4 (Table 1B) showed no significance at a single time point. Analysis of change over time reveals a significant interaction between CVD Risk and XP3 as well as XP4 with p-value of 0.008 and 0.03 respectively. Within XP3 for intermediate exposure was significantly associated with increased CVD risk over time ( $p=0.015$ ) and trended to significance for XP4 ( $p=0.054$ ).

**Conclusions:** A significant effect is seen between PM and increased CVD risk over time. These findings suggest that the level of chronic lower levels of exposure may have greater impact on CVD risk compared with acute intense PM exposure.

## 5. Serum Perfluoroalkyl Substances and Cardiometabolic Consequences in Adolescents Exposed to the World Trade Center Disaster and a Matched Comparison Group

Koshy, T. T., Attina, T. M., Ghassabian, A., Gilbert, J., Burdine, L. K., Marmor, M., Honda, M., Chu, D. B., Han, X., Shao, Y., Kannan, K., Urbina, E. M., & Trasande, L. (2017). Serum perfluoroalkyl substances and cardiometabolic consequences in adolescents exposed to the World Trade Center disaster and a matched comparison group, *Environment International*, 109, 128-135.  
<https://doi.org/10.1016/j.envint.2017.08.003>.

### Abstract

**Background:** Large amounts of various chemical contaminants, including perfluoroalkyl substances (PFASs), were released at the time of the World Trade Center (WTC) disaster. Thousands of children who lived and/or attended school near the disaster site were exposed to these substances but few studies have examined the possible consequences related to these exposures.

**Objectives:** To examine the relationship of PFASs serum levels with cardiometabolic profile in children and adolescents enrolled in the World Trade Center Health Registry (WTCHR) and a matched comparison group.

**Methods:** We evaluated WTCHR enrollees who resided in New York City and were born between September 11, 1993, and September 10, 2001, and a matched comparison group consisting of individuals who were ineligible for WTCHR participation upon distance of their home, school or work from the WTC and lack of participation in rescue and recovery activities. Matching was based on date of birth, sex, race, ethnicity, and income. We assessed exposure to PFASs, as measured by serum levels and association with cardiometabolic profile as measured by arterial wall stiffness, body mass index, insulin resistance, fasting total cholesterol, HDL, LDL, and triglycerides.

**Results:** A total of 402 participants completed the study and serum samples were analyzed from 308 participants, 123 in the WTCHR group and 185 in the comparison group. In multivariable regression analysis, after adjusting for relevant confounders, we observed a significant, positive association of perfluorooctanoic acid (PFOA) with triglycerides (beta coefficient = 0.14, 95% CI: 0.02, 0.27, 15.1%

change), total cholesterol (beta coefficient = 0.09, 95% CI: 0.04, 0.14, 9.2% change), and LDL cholesterol (beta coefficient = 0.11, 95% CI: 0.03, 0.19, 11.5% change). Perfluorohexanesulfonic acid levels were associated with decreased insulin resistance (beta coefficient = - 0.09, 95% CI: - 0.18, - 0.003, - 8.6% change); PFOA and perfluorononanoic acid were associated with increased brachial artery distensibility.

**Conclusions:** This research adds to our knowledge of the physical health impacts in a large group of children exposed to the WTC disaster. Abnormal lipid levels in young adults might be an early marker of atherosclerosis and cardiovascular diseases and our findings highlight the importance of conducting longitudinal studies in this population.

## 6. Health Effects Following Exposure to Dust from the World Trade Center Disaster: An Update

Mears, M. J., Aslaner, D. J., Barson, C. T., Cohen, M. D., Gorr, M. W., & Wold, L. E. (2022). Health effects following exposure to dust from the World Trade Center disaster: An update. *Life Sciences*, 289. <https://doi.org/10.1016/j.lfs.2021.120147>.

### Abstract

Exposure to dust, smoke, and fumes containing volatile chemicals and particulate matter (PM) from the World Trade Center (WTC) towers' collapse impacted thousands of citizens and first responders (FR; firefighters, medicals staff, police officers) of New York City. Surviving FR and recovery workers are increasingly prone to age-related diseases that their prior WTC dust exposures might expedite or make worse. This review provides an overview of published WTC studies concerning FR/recovery workers' exposure and causal mechanisms of age-related disease susceptibility, specifically those involving the cardiopulmonary and neurological systems. This review also highlights the recent findings of the major health effects of cardiovascular, pulmonary, and neurological health sequelae from WTC dust exposure. To better treat those that risked their lives during and after the disaster of September 11, 2001, the deleterious mechanisms that WTC dust exposure exerted and continue to exert on the heart, lungs, and brain of FR must be better understood.

## 7. The Prevalence of Metabolic Syndrome Among Law Enforcement Officers Who Responded to the 9/11 World Trade Center Attacks

Moline, J. M., McLaughlin, M. A., Sawit, S. T., Maceda, C., Croft, L. B., Goldman, M. E., Garcia, M. J., Iyengar, R. L. & Woodward, M. (2016). The prevalence of metabolic syndrome among law enforcement officers who responded to the 9/11 World Trade Center attacks. *Am. J. Ind. Med.*, 59, 752-760. <https://doi.org/10.1002/ajim.22649>

### Abstract

**Background:** Law enforcement officers (LEOs) experience high rates of cardiovascular events compared with the general US population. Metabolic syndrome (MetS) confers an increased risk of cardiovascular disease and all-cause mortality. Data regarding MetS among LEOs are limited.

**Methods:** We sought to determine the prevalence of MetS and its associated risk factors as well as gender differences among LEOs who participated in the World Trade Center (WTC) Law Enforcement Cardiovascular Screening (LECS) Program from 2008 to 2010. We evaluated a total of 2,497 participants, 40 years and older, who responded to the 9/11 WTC attacks.

**Results:** The prevalence of MetS was 27%, with abdominal obesity and hypertension being the most frequently occurring risk factors. MetS and its risk factors were significantly higher among male compared to female LEOs, except for reduced HDL-cholesterol levels.

**Conclusions:** MetS is a rising epidemic in the United States, and importantly, approximately one in four LEOs who worked at the WTC site after 9/11 are affected. *Am. J. Ind. Med.* 59:752–760, 2016. © 2016 Wiley Periodicals, Inc.

#### **8. Post-Traumatic Stress Disorder and Cardiovascular Diseases: A Cohort Study of Men and Women Involved in Cleaning the Debris of the World Trade Center Complex**

Remch, M., Laskaris, Z., Flory, J., Mora-McLaughlin, C., & Morabia, A. (2018). Post-traumatic stress disorder and cardiovascular diseases: A cohort study of men and women involved in cleaning the debris of the World Trade Center complex. *Circulation: Cardiovascular Quality and Outcomes*, 11. <https://doi.org/10.1161/CIRCOUTCOMES.117.004572>

##### **Abstract**

**Background:** We sought to determine whether post-traumatic stress disorder (PTSD) is a risk factor for myocardial infarction (MI) and stroke, beyond the expected effects from recognized cardiovascular risk factors and depression.

**Methods and Results:** World Trade Center–Heart is an observational prospective cohort study of 6481 blue-collar first responders nested within the World Trade Center Health Program in New York City. Baseline measures in 2012 and 2013 included blood pressure, weight and height, and blood lipids. PTSD, depression, smoking, and dust exposure during the 2001 cleanup were self-reported. During the 4-year follow-up, outcomes were assessed through (1) interview-based incident, nonfatal MI, and stroke, validated in medical charts (n=118); and (2) hospitalizations for MI and stroke for New York city and state residents (n=180). Prevalence of PTSD was 19.9% in men and 25.9% in women, that is, at least twice that of the general population. Cumulative incidence of MI or stroke was consistently larger for men or women with PTSD across follow-up. Adjusted hazard ratios (HRs) were 2.22 (95% confidence interval [CI], 1.30–3.82) for MI and 2.51 (95% CI, 1.39–4.57) for stroke. For pooled MI and stroke, adjusted HRs were 2.35 (95% CI, 1.57–3.52) in all and 1.88 (95% CI, 1.01–3.49) in men free of depression. Using hospitalization registry data, adjusted HRs were 2.17 (95% CI, 1.41–3.32) for MI; 3.01 (95% CI, 1.84–4.93) for stroke; and for pooled MI and stroke, the adjusted HR was 2.40 (95% CI, 1.73–3.34) in all, HR was 2.44 (95% CI, 1.05–5.55) in women, and adjusted HR was 2.27 (95% CI, 1.41–3.67) in men free of depression. World Trade Center dust exposure had no effect.

**Conclusions:** This cohort study confirms that PTSD is a risk factor for MI and stroke of similar magnitude in men and women, independent of depression.

#### **9. Cardiovascular Disease in the World Trade Center Health Program General Responder Cohort**

Sloan, N. L., Shapiro, M. Z., Sabra, A., et al. (2021). Cardiovascular disease in the World Trade Center Health Program general responder cohort. *Am J Ind Med*, 64, 97– 107. <https://doi.org/10.1002/ajim.23207>

## Abstract

### Background

Over 90,000 rescue and recovery responders to the September 2001 World Trade Center (WTC) attacks were exposed to toxic materials that can impair cardiac function and increase cardiovascular disease (CVD) risk. We examined WTC-related exposures association with annual and cumulative CVD incidence and risk over 17 years in the WTC Health Program (HP) General Responder Cohort (GRC).

### Methods

Post 9/11 first occurrence of CVD was assessed in 37,725 responders from self-reported physician diagnosis of, or current treatment for, coronary artery disease, myocardial infarction, stroke and/or congestive heart failure from WTCHP GRC monitoring visits. Kaplan–Meier estimates of CVD incidence used the generalized Wilcoxon test statistic to account for censored data. Cox proportional hazards regression analyses estimated the CVD hazard ratio associated with 9/11/2001 arrival in responders with and without dust cloud exposure, compared with arrival on or after 9/12/2001. Additional analyses adjusted for comorbidities.

### Results

To date, 6.3% reported new CVD. In covariate-adjusted analyses, men's CVD 9/11/2001 arrival risks were 1.40 (95% confidence interval [CI] = 1.26, 1.56) and 1.43 (95% CI = 1.29, 1.58) and women's were 2.16 (95% CI = 1.49, 3.11) and 1.59 (95% CI = 1.11, 2.27) with and without dust cloud exposure, respectively. Protective service employment on 9/11 had higher CVD risk.

### Conclusions

WTCHP GRC members with 9/11/2001 exposures had substantially higher CVD risk than those initiating work afterward, consistent with observations among WTC-exposed New York City firefighters. Women's risk was greater than that of men's. GRC-elevated CVD risk may also be occurring at a younger age than in the general population.

## Peer-Reviewed In Vivo Research: Cardiovascular Disease and WTC Toxin Exposure

### 1. Longitudinal Impact of WTC Dust Inhalation on Rat Cardiac Tissue Transcriptomic Profiles

Park, S. H., Lu, Y., Shao, Y., Prophete, C., Horton, L., Sisco, M., Lee, H. W., Kluz, T., Sun, H. Costa, M., Zelikoff, J., Chen, L. C., Gorr, M. W., Wold, L. E., & Cohen, M. D. (2022). Longitudinal impact of WTC dust inhalation on rat cardiac tissue transcriptomic profiles. *International Journal of Environmental Research and Public Health*, 19(2)9, 19. <https://doi.org/10.3390/ijerph19020919>

#### Abstract

First responders (FR) exposed to the World Trade Center (WTC) Ground Zero air over the first week after the 9/11 disaster have an increased heart disease incidence compared to unexposed FR and the general population. To test if WTC dusts were causative agents, rats were exposed to WTC dusts (under isoflurane [ISO] anesthesia) 2 h/day on 2 consecutive days; controls received air/ISO or air only. Hearts were collected 1, 30, 240, and 360 d post-exposure, left ventricle total RNA was extracted, and transcription profiles were obtained. The data showed that differentially expressed genes (DEG) for WTC

vs. ISO rats did not reach any significance with a false discovery rate (FDR)  $< 0.05$  at days 1, 30, and 240, indicating that the dusts did not impart effects beyond any from ISO. However, at day 360, 14 DEG with a low FDR were identified, reflecting potential long-term effects from WTC dust alone, and the majority of these DEG have been implicated as having an impact on heart functions. Furthermore, the functional gene set enrichment analysis (GSEA) data at day 360 showed that WTC dust could potentially impact the myocardial energy metabolism via PPAR signaling and heart valve development. This is the first study showing that WTC dust could significantly affect some genes that are associated with the heart/CV system, in the long term. Even  $> 20$  years after the 9/11 disaster, this has potentially important implications for those FR exposed repeatedly at Ground Zero over the first week after the buildings collapsed.

### **Conclusions**

The results of this study showed that repeated exposures to Ground Zero WTC dust were able to impact changes in gene expression in the hearts of exposed rats. More importantly, any 'pure' effects from the dusts did not manifest until a significant time had elapsed from the exposures themselves. Even  $> 20$  years after the 9/11 disaster, this has potentially important implications for those FR who were exposed repeatedly to these dusts at Ground Zero during the first week after the buildings collapsed. Of note, the WTC dust was found to affect gene expression that could influence a variety of heart/cardiovascular functions, including coronary artery disease, heart development, cardiac fibrosis, myocardial hypertrophy, myocardial infarct, heart failure, etc. The WTC dust effect in the presence of potential ISO–WTC dust interactions could potentially impact the myocardial energy metabolism via PPAR signaling and heart valve development.

The authors are cognizant of several important limitations to these studies. As noted in the Methods, the co-exposure of the rats to ISO and the dust resulted in confounding outcomes. A new exposure method is being developed that will not require ISO, therefore it will allow for equivalent WTC dust delivery into the lungs and will reiterate many of the outcomes seen here. The co-exposure effect has meant that the ISO might have negatively impacted (or conversely, amplified) the magnitude of any given WTC dust effect so that some dust effects could not be clearly discerned or defined as significant. It is also possible that WTC dust modulated any true effects of ISO on gene expressions. All attempts were made here to disentangle the confounding from the true effects of both the WTC dust and the ISO. Another limitation was that only a single dust dose that would approximate Ground Zero air levels of  $\approx 250$  mg dust/m<sup>3</sup> was used. While dust levels were  $\geq 1000$  mg/m<sup>3</sup> at Ground Zero in the first hours after the disaster, and a significant number of FR were exposed to such levels in that period, most of the exposed FR arrived on scene in the hours after when levels dropped to 100s of mg/m<sup>3</sup> and stayed on-site for periods where air dust levels remained in this range. Further, exposures of rats to WTC dusts at levels that would reflect any FR exposures at  $\geq 1000$  mg/m<sup>3</sup> have proven to be moreover lethal in the 2 h/day, 2-day paradigm that mimics the 'reference FR.' As a result, no useful long-term, post-exposure data from those rats could be obtained. Lastly, another key limitation here was that studies did not go further to determine if any observed effects manifest even beyond the 1-year post-exposure timepoint or the earlier effects persisted long term. The nature of this study was that several early timepoints (i.e., days 1 and 30) had to be evaluated to establish baseline outcomes (early-onset, short-lived, etc.). Based on the pool of results presented here, the next series of studies will have rats dedicated for the examination at far later timepoints (i.e., up to 2-year post-exposure) and only a few examined at those early timepoints (to confirm reproducibility of outcomes).

## 2. Exposure to WTC Dust Alters Rat Cardiac Gap Junctional Proteins

Tanwar, V., Bhattacharya, S., Rustagi, S., Bulgart, H., Cohen, M., & Wold, L. S. (2019). Exposure to WTC dust alters rat cardiac gap junctional proteins. *The FASEB Journal*, 33: 531.15. [https://doi.org/10.1096/fasebj.2019.33.1\\_supplement.531.15](https://doi.org/10.1096/fasebj.2019.33.1_supplement.531.15)

### Abstract

**Objective:** First responders (FR) present at Ground Zero during the first 72 h after the World Trade Center (WTC) towers collapsed have exhibited increased incidences of cardiovascular disease (CVD) risk. Despite increasing evidence of CVDs, the mechanistic underpinnings behind adverse effects of WTC dust exposure are not well studied. Using a system that generated/delivered supercoarse (10–53  $\mu\text{m}$ ) WTC dusts (in a manner that mimicked FR exposures), this study sought to examine potential toxicities in the heart.

**Methods:** In this study, rats were exposed on two consecutive days for 2 h/day by intratracheal inhalation (ITIH) to supercoarse (10–53  $\mu\text{m}$ ) WTC dusts (while under isoflurane [ISO] anesthesia) or an air/ISO (naïve) mixture. This dose conservatively modeled likely exposures to nearly  $\approx 250$  mg dust/m<sup>3</sup> FR exposure. Hearts were harvested 30- & 60-days post-exposure and processed for qualitative and quantitative protein expression analyses.

**Results:** Data obtained from right ventricular samples demonstrate decreased desmin expression in the WTC exposed group as compared to the control groups (naïve and ISO). Interestingly, although no change in the expression of connexin-43 was observed between the exposed and control groups, localization studies using confocal microscopy revealed disrupted organization of connexin-43 at the cardiomyocyte junction. Additionally, confocal imaging suggested reduction of F-actin expression in the WTC exposed group compared to control groups. Further, expression profiles of the PI3K/Akt signaling axis using western blot analysis revealed a marked decrease in activated phospho-Akt in the WTC dust exposed group in comparison to control groups. Although blunted activation of Akt was observed, phospho-PI3K levels were unaltered.

**Conclusion:** Exposure to WTC dusts caused significant remodeling of gap junctions and altered expression of selected mechanical junction proteins at the intercalated disks. These results illustrate that a defect in a structural/gap junction protein can cause alterations in structural integrity leading to electrical and mechanical perturbations that can contribute to cardiac dysfunction.

## 3. World Trade Center-Cardiorespiratory and Vascular Dysfunction: Assessing the Phenotype and Metabolome of a Murine Particulate Matter Exposure Model

Veerappan, A., Oskuei, A., Crowley, G. et al. (2020). World Trade Center-cardiorespiratory and vascular dysfunction: Assessing the phenotype and metabolome of a murine particulate matter exposure model. *Sci Rep*, 10, 3130. <https://doi.org/10.1038/s41598-020-58717-w>

### Abstract

Vascular changes occur early in the development of obstructive airways disease. However, the vascular remodeling and dysfunction due to World Trade Center-Particulate Matter (WTC-PM) exposure are not well described and are therefore the focus of this investigation. C57Bl/6 female mice oropharyngeally aspirated 200  $\mu\text{g}$  of WTC-PM53 or phosphate-buffered saline (PBS) (controls). 24-hours (24-hrs) and 1-

Month (1-M) after exposure, echocardiography, micro-positron emission tomography( $\mu$ -PET), collagen quantification, lung metabolomics, assessment of antioxidant potential and soluble-receptor for advanced glycation end products (sRAGE) in bronchoalveolar lavage (BAL) and plasma were performed. 24-hrs post-exposure, there was a significant reduction in (1) Pulmonary artery (PA) flow-velocity and pulmonary ejection time (PET) (2) Pulmonary acceleration time (PAT) and PAT/PET, while (3) Aortic ejection time(AET) and velocity time integral(VTI) were increased, and (4) Aortic acceleration time (AAT)/AET, cardiac output and stroke volume were decreased compared to controls. 1-M post-exposure, there was also significant reduction of right ventricular diameter as right ventricle free wall thickness was increased and an increase in tricuspid E, A peaks and an elevated E/A. The pulmonary and cardiac standard uptake value and volume 1-M post-exposure was significantly elevated after PM-exposure. Similarly,  $\alpha$ -smooth muscle actin( $\alpha$ -SMA) expression, aortic collagen deposition was elevated 1-M after PM exposure. In assessment of the metabolome, prominent subpathways included advanced glycation end products (AGEs), phosphatidylcholines, sphingolipids, saturated/unsaturated fatty acids, eicosanoids, and phospholipids. BAL superoxide dismutase (SOD), plasma total-antioxidant capacity activity, and sRAGE (BAL and plasma) were elevated after 24-hrs. PM exposure and associated vascular disease are a global health burden. Our study shows persistent WTC-Cardiorespiratory and Vascular Dysfunction (WTC-CaRVD), inflammatory changes and attenuation of antioxidant potential after PM exposure. Early detection of vascular disease is crucial to preventing cardiovascular deaths and future work will focus on further identification of bioactive therapeutic targets.